The Ocular Surface 24 (2022) 22–30

Contents lists available at ScienceDirect

The Ocular Surface

journal homepage: www.elsevier.com/locate/jtos

Special Issue: Infections

Fungal keratitis: A review of clinical presentations, treatment strategies and outcomes

Namrata Sharma [a,*], Bhupesh Bagga [b], Deepali Singhal [c], Ritu Nagpal [a], Anahita Kate [d], Gunjan Saluja [e], Prafulla K. Maharana [a]

[a] Cornea, Cataract & Refractive Surgery Services, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India
[b] The Cornea Institute, LV Prasad Eye Institute, Hyderabad, India
[c] ASG Eye Hospitals, Bhubaneshwar, India
[d] The Cornea Institute, LV Prasad Eye Institute, Vijaywada, India
[e] Strabismus, Oculoplasty & Neuro-ophthalmology Services, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India

ARTICLE INFO

Keywords:
Fungal keratitis
Natamycin
Voriconazole
Intrastromal voriconazole
TST protocol
MUTT Trial
Rose bengal PDAT

ABSTRACT

Infectious keratitis is a significant cause of corneal blindness worldwide. Although less prevalent in the developed world, cases of fungal keratitis account for almost half of all keratitis cases, occurring in the developing countries. These cases are one of the most refractory types of infectious keratitis and present various challenges to the treating physician such as delayed presentation, long waiting time for culture positivity, limited availability effective antifungal drugs, prolonged duration for response to therapy, a highly variable spectrum of antifungal drug sensitivity and a high recurrence rate following keratoplasty. The advent of rapid diagnostic tools, molecular methods, in vitro anti-fungal drug sensitivity testing, alternatives to natamycin, targeted drug delivery and most importantly the results of large randomized controlled trials have significantly improved our understanding and approach towards the diagnosis and management of cases with fungal keratitis.

Overall, *Aspergillus and Fusarium* species are the most common causes ones of fungal keratitis. History of antecedent trauma is a significant predisposing factor. Corneal scrapings for microscopic evaluation and culture preparation, is the standard of care for establishing the diagnosis of fungal keratitis. Molecular identification of cultures offers accurate identification of fungal pathogens, especially the rare species. Natamycin is an approved first-line drug. Voriconazole is the best alternative, especially for non-fusarium cases. Management involves administration of drugs usually by a combination of various routes, the treatment regimen being individualized depending upon the response to therapy. Photodynamic therapy is a newer treatment modality, being tried for non-responsive cases, before resorting to a therapeutic graft.

1. Introduction

Mycotic keratitis is a leading cause of ocular morbidity throughout the world, particularly in tropical and subtropical countries [1,2]. According to World Health Organization; 2001 survey, corneal blindness is the second major cause of blindness after cataract [3]. Furthermore, ocular trauma and corneal ulceration are amongst the most important causes of corneal blindness, especially in developing countries. Gonzales et al. reported that the annual incidence of corneal ulceration in Madurai District of South India was 113 per 10^5 people, which was 10 times the annual incidence reported from Olmsted County, Minnesota, in the United States of America [4,5]. Keeping these figures in mind, corneal ulceration has been recognized as a silent epidemic in the developing countries [3]. Fungal keratitis carries a relatively poor prognosis, compared to other forms of infectious keratitis due to various reasons such as delayed microbiological identification, sub-optimal efficacy and penetration of antifungal agents, morphologic pleomorphism in cultures and a very wide spectrum of drug sensitivity with the existing medications. It is a serious public health problem affecting the agrarian poor and hence requires special attention. Various risk factors, etiologies, diagnostic methods, and treatment strategies have been discussed in this review.

* Corresponding author. Dr. R.P Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, 110029.
E-mail address: namrata.sharma@gmail.com (N. Sharma).

https://doi.org/10.1016/j.jtos.2021.12.001
Received 31 July 2021; Received in revised form 20 November 2021; Accepted 2 December 2021
Available online 13 December 2021
1542-0124/

Table 1
Risk factors for occurrence of fungal keratitis.

Ocular factors		Systemic factors
Trauma	Vegetative & organic matter	Diabetes mellitus
Chronic corneal inflammation	Herpes simplex	HIV positivity
	Herpes zoster	Leprosy
	Vernal keratoconjunctivitis	Diabetes mellitus
	Ocular surface Disease	
	Dry eye	
	Bullous keratopathy	
	Exposure Keratopathy	
Contact lens wear	Poor hygiene	
Drugs	Corticosteroids	
	Topical anesthetic abuse	
Prior Corneal surgery	Keratoplasty	
	Refractive surgery	

Table 2
Fungal pathogens implicated in the causation of infective keratitis in humans.

Filamentous			Yeast
Septate		Non-septate	*Candidia albicans, parapsilosis, krusei, tropicalis*
Nonpigmented	**Pigmented**	*Rhizopus (mucormycosis)*	
Fusarium solani, oxysporum, moniliforme, episphaesia, nivale	*Curvularia senegelensis, verruculosa, pallescens*		
Aspergillus fumigatus, flavus	*Lasiodiplodia theobromae*		
Acremonium (Cephalosporium)	*Alternaria*		
Paecilomyces	*Cladosporium*		
Penicillium	*Celletotrichum*		

2. Risk factors

The predisposing factors can be either ocular or systemic (Table 1). Fungal keratitis is most commonly exogenous in origin, usually resulting from traumatic implantation of fungal fragments or spores in to the surface layers of cornea. Trauma with vegetative matter is the accounting for approximately 55–65% of all fungal keratitis cases [1,6]. The increasing use of contact lenses in recent years, has contributed to be an important factor for fungal keratitis cases, particularly in the developed countries. Other associated ocular factors include use of topical medications such as corticosteroids, presence of underlying ocular surface disease, bullous keratopathy, exposure keratopathy, and prior ocular surgery such as a refractive procedure. Systemic risk factors include presence of diabetes mellitus and immunosuppression. Filamentous fungi have been reported to be more commonly associated with vegetative matter injury, while yeasts have been implicated in immunocompromised patients and are more common in developed countries [7]. Factors found to be associated with poor visual outcome include large and deep ulcers, pigmented ulcers, older age of patient, male gender, and infection with *Aspergillus* species [8].

3. Etiology

Fungal pathogens involved in the causation of infective keratitis can be grouped in four classes – Filamentous septate, Filamentous non-septate, yeasts, and others (Table 2). These organisms can also be classified as *Moniliaceae (*non-pigmented filamentary fungi, including *Fusarium* and *Aspergillus species), Dematiaceae* (pigmented filamentary fungi including *Curvularia* and *Lasiodiplodia species*), yeasts; including *Candida* species and other fungi. Most of the fungi associated with keratitis are saprophytic. Filamentous fungi are the primary etiological agents involved in causation of keratitis, in the developing countries. The common pathogenic species include *Aspergillus, Fusarium, Candida, Curvularia*, and *Penicillium*, among which *Fusarium* (37–62%) and *Aspergillus* (24–30%) are the most common ones [1]. *Dematiaceous* fungi contribute to around 8–16.7% cases of fungal keratitis.

Table 3
Prevalence of fungal keratitis based on culture results and common etiological agents in various parts of world.

Author, year	Location	Prevalence (%)	Commonest organism
Lin et al. [54], 2012	South India	36.5	*Fusarium* spp.
Ghosh et al. [55], 2016	North India	16	*Aspergillus* spp.
Dutta et al. [56], 1981	East India	32	*Aspergillus* spp.
Verenkar et al. [57], 1998	West India	16.4	*Aspergillus* spp.
Feilmeier et al. [58], 2010	Nepal	24.1	*Aspergillus* spp.
Alkatan et al. [59], 2012	Saudi Arabia	3.8	*Aspergillus* spp. and *Candida* spp.
Xie et al. [60], 2006	North China	56.4	*Fusarium* spp.
Boonpasart et al. [61], 2002	Thailand	11.6	*Fusarium* spp.
Yilmaz et al. [62], 2007	Turkey	8.0	*Fusarium* spp.
Toshida et al. [63], 2007	Japan	4.8	*Candida* spp.
Cariello et al. [64], 2011	Brazil	5.3	*Fusarium* spp.
Ritterband et al. [65], 2006	USA, New York	1.2	*Candida* spp.
Liesegang et al. [66], 1980	USA, South Florida	20.2	*Fusarium* spp.
Dunlop et al. [67], 1994	Bangladesh	35.9	*Aspergillus* spp.
Thew et al. [68], 2008	Australia	16.8	*Fusarium* spp.
Ebadollahi- Natanzi et al. [69], 2016	Iran	5.5	*Fusarium* spp.

Table 4
Clinical features of fungal keratitis.

A. Non-specific features
1. Conjunctival injection
2. Epithelial defect
3. Anterior chamber reaction
B. Specific features
1. Deep stromal infiltrate
2. Feathery margins
3. Gray/brown pigmentation
4. Dry looking rough texture
5. Satellite lesions

The prevalence of fungal keratitis varies widely and is influenced by variations in geography, climate, age, gender, socioeconomic status, agricultural activity, and the extent of urbanization(Table 3). [9] *Aspergillus, Fusarium,* and *Curvularia* species are predominantly found in tropical areas whereas, yeasts are common in temperate areas of the world. The prevalence of *Candida* keratitis is reported to be 60.6% in London and 32.7% in Melbourne [10]. *Acremonium* spp. are the primary pathogens reported from Paraguay [10]. Prajna et al. reported *Aspergillus* species, to be the commonest etiologies from the Northern and Eastern regions of India, while *Fusarium* species, as the commonest organisms in the Western and Southern parts of country [7].

4. Cinical features

Clinical diagnosis of fungal keratitis is often challenging. It should be made based on a careful evaluation of patient's history, examination, and laboratory investigations (Table 4). Bharathi et al. have reported the clinical features and epidemiology of fungal keratitis in 1095 patients in South India [11]. The incidence of fungal keratitis was found to be more

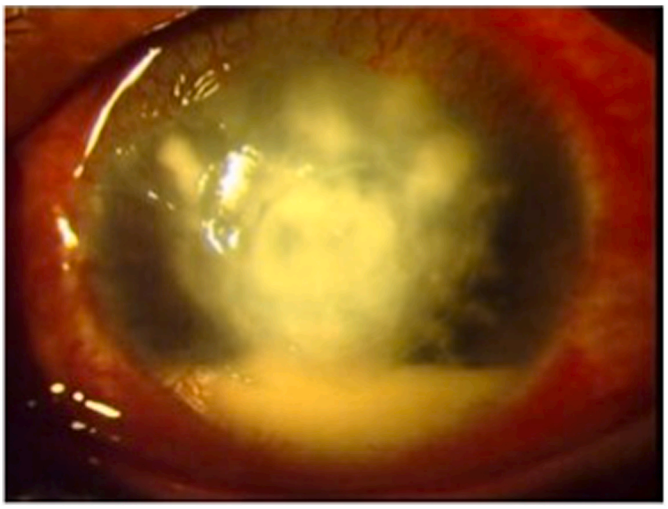

Fig. 1. Illustration of a typical case of fungal keratitis with feathery margins and hypopyon.

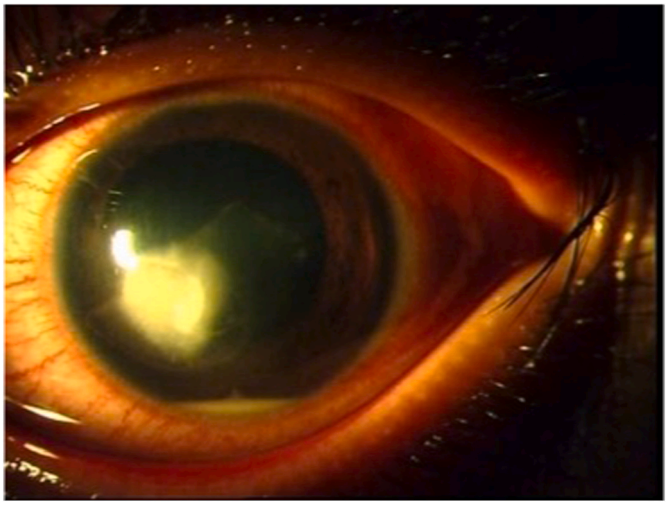

Fig. 2. A case of candida fungal keratitis with collar button appearance and surrounding infiltrates.

in males belonging to the age group, between 21 and 50 years.

4.1. Symptoms

Patients of fungal keratitis usually present with insidious onset and gradual progression of symptoms of, pain, watering, photophobia, foreign body sensation and diminution of vision. Symptoms at presentation are minimal with a comparatively longer duration, compared to cases with bacterial keratitis. Visual acuity depends upon the location of the corneal lesion, which can be either central (central 4 mm), paracentral (4–8 mm), or peripheral (beyond 8 mm).

4.2. Signs

Similar to symptoms, the severity of signs is also less compared to bacterial keratitis. Various signs include lid edema, conjunctival injection, chemosis, presence of an epithelial defect and underlying stromal infiltrate. Classically, the fungal corneal ulcer has been described as a dry looking ulcer with a gray-white infiltrate, and creamy exudates at its base. Other characteristic findings include feathery margins seen in approximately 70% of cases and satellite lesions, which are observed in around 10% cases [1,11]. (Fig. 1) Presence of a fixed hypopyon (no change in position after 10 min of lying supine) is also a common feature, seen in about 45–66% of cases [12]. However, not all fungal ulcers demonstrate these characteristic signs. Other features include presence of an immune ring, deep stromal abscess, and an endothelial plaque. The corneal epithelium over the deep seated stromal infiltrates

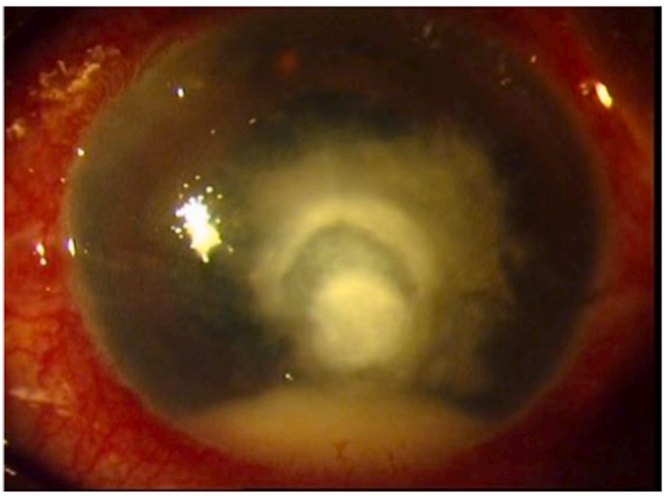

Fig. 3. A case of fungal keratitis with central corneal thinning and surrounding infiltrates with hypopyon.

Table-5
Classification and mechanism of action of currently available antifungal medications.

Class	Mechanism of Action	Sub-class	Examples
Polyenes	Formation of pores and alteration in cell permeability by acting on ergosterol leading to extrusion of vital cytoplasmic content	Large Polyenes Small Polyenes	Nystatin Amphotericin B Natamycin
Azoles	Inhibition of 14α-sterol demethylase leading to altered cell membrane permeability and lysis.	Imidazoles Triazoles	Topical - Miconazole, Clotrimazole, Econazole, Oxiconazole Systemic – Ketoconazole Topical- Voriconazole, Posaconazole Systemic - Fluconazole, Itraconazole, Voriconazole, Posaconazole, Ravuconazole
Pyrimidine	Interferes with pyrimidine metabolism, RNA, DNA, and protein synthesis		5- Flucytosine
Allylamine	Inhibition of Squalene epoxidase, Inhibition of the ergosterol synthesis leading to altered cell membrane permeability and cell lysis		Terbinafine
Echinocandins	Inhibits the beta-(1,3)- D-glucan synthase leading to increased cell wall permeability and cell lysis		Caspofungin, Micafungin, Anidulafungin
Heterocyclic Benzofurans	Interferes with the microtubule assembly		Griseofulvin

Table 6
Preparations of commonly used antifungal drugs.

Drug	Route	Concentrati on	Preparatio n	Storage	Stability
Voriconazo le	Topical	1%	Mix 20 ml ringer lactate to 200 mg voriconazo le lyophilized powder	Refrigerate or room temperatur e	30 days at 4° C or room temperatu re
	Intrastro mal	50 μgm/0.1 ml or 0.05 mg/ml	Mix 20 ml ringer lactate to 200 mg voriconazo le lyophilized powder. Take 1 ml, from this and add 19 ml ringer lactate to it	Immediate use	Immediat e use
	Intracame ral	50 μgm/0.1 ml or 0.05 mg/ml	Same as intrastrom al	Immediate use	Immediat e use
Amphoteri cin B	Topical	0.15%	Add 10 ml distilled or sterile water to parenteral 50 mg of amphotericin B powder for injection. Draw 3 ml of this and add to 7 ml of artificial tears eye drops.	Should not be exposed to light. The drops Should be inspected at each visit for any turbidity, which may indicate contaminati on or drug precipitatio n.	7 days in refrigerator at 4° C and 4 days in room temperatu re
	Intrastro mal	5 -10 μgm/0.1 ml or 0.1mg/1 ml	Add 10 ml distilled or sterile water to parenteral 50 mg of amphoteri cin B powder for injection. Take 0.2 ml from this solution and add 0.8 ml BSS or sterile water. Take 0.1 ml of this solution and add 0.9 ml BSS or Sterile water to it.	Immediate use	Immediat e use
	Intracameral	5–10 μgm/0.1 ml or 0.1mg/1 ml	Same as intrastrom al	Immediate use	Immediat e use

might be intact. *Candida* keratitis often presents with a "collar button" configuration of infiltrates (Fig. 2). *Dematiacious* fungi can present with both superficial and deep seated ulcers and have a characteristic gray or brown pigmentation. This pigmented appearance is due to the alteration in melanin metabolism and indicates a more superficial location of infection caused by a low virulent organism inciting a comparatively lesser inflammatory reaction.

This first signs usually take several hours or days to develop after the inciting factor, which can be either trauma or contact lens use. Virulent fungi such as *Aspergillus* or *Fusarium species* might lead to rapid progression with consequent corneal perforation and endophthalmitis, especially when corticosteroids have been prescribed. Other complications include stromal melt, descemetocele formation, scleritis, ocular hypertension or hypotony, endophthalmitis, panophthalmitis and orbital cellulitis (Fig. 3).

5. Management

Management of fungal keratitis is challenging. Poor ocular penetration and low bioavailability of the currently available antifungal agents to the desired site of action are the primary causes of poor outcome, in most cases. Other factors include delayed presentation, longer time for cultures to be positive and subsequently delay in determination of antifungal drug sensitivity pattern, and inability of the first line drugs to cover most fungal pathogens.

5.1. Antifungal drugs

The currently available antifungal drugs and their modes of action have been summarized in Table 5. These are broadly classified as polyenes, azoles, pyrimidines, allylamines, echinocandins and heterocyclic benzofurans. Polyenes and azoles are the most commonly used antifungal drugs in clinical practice [13–20]. The first line of therapy of fungal keratitis is to start with topical antifungals. The role of systemic antifungal drugs is controversial. Natamycin (NTM), and Voriconazole (VCZ) are the two most commonly prescribed drugs. Other antifungal agents include Amphotericin B (AMB), ketoconazole (KCZ), itraconazole (ICZ), and fluconazole (FCZ) [14,21–23].

6. Natamycin (NTM)

Natamycin is the most commonly prescribed topical antifungal drug. It is the only drug currently approved by the United States Food and Drug Administration (USFDA) to treat mycotic keratitis. NTM is produced by the bacteria *Streptomyces natalensis* [24]. Commercially it is available in a suspension formulation (5%, 50 mg/ml) and therefore needs to be shaken well before administration. It has a broad spectrum of antifungal activity, and works well against various fungal species such as *Fusarium*, *Aspergillus, Alternaria*, *Candida, Cephalosporium*, *Colletotrichum*, *Curvularia*, *Lasiodiplodia*, *Scedosporium*, *Trichophyton*, and *Penicillium* [25]. It is usually started at a frequency of one drop, instilled every one -two hourly interval at the beginning of therapy. Subsequently, the frequency is reduced depending upon the clinical response. Once clinical resolution of keratitis is achieved, it is advised to continue topical therapy for a period of at least four weeks, at a frequency of four times per day. Few authors recommend concurrent corneal epithelial debridement to increase the penetration of NTM. However, in a multicentric double-masked clinical trial comparing topical NTM and topical VCZ in 120 patients by Prajna et al. the authors found no difference in the healing time, when epithelial debridement was performed done in addition to topical therapy in either group. On the contrary, worse visual outcomes were was noted in the sub-group wherein epithelial debridement was performed [26].

The clinical efficacy of Natamycin is well documented in the literature. The Mycotic Ulcer Treatment Trial-1 (MUTT-1) compared topical NTM with VCZ in a multi-centric randomized clinical trial. The trial included 368 patients with smear-positive filamentous fungal ulcers with best corrected visual acuity (BCVA) ranging from 20/40 to 20/400. The authors found patients receiving NTM to have better BCVA and a lower perforation rate than patients who received VCZ at 3 months follow-up [27]. Further, it was found that the difference was significant among the *Fusarium* cases (40% of the study participants) while the non-Fusarium cases (*Aspergillus*- 17%, and others- 43%) fared similarly with either drug [27].

NTM is known to be an epitheliotoxic drug, when used for a prolonged duration of time. Various side effects include redness, foreign body sensation, stinging and burning sensation, and tearing. Besides, the suspended particles remain stuck to the area of epithelial defect, in the fornices and along the lid margins.

7. Voriconazole

Voriconazole (VCZ) is the second-best topical drug available for the treatment of fungal keratitis. It is available in both oral and parenteral

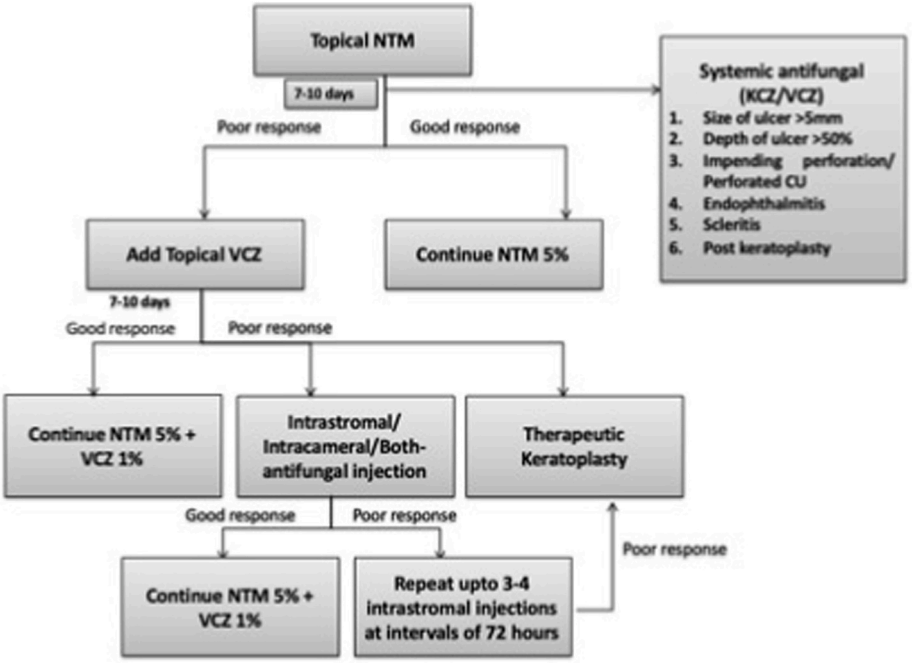

Fig. 4. Figure showing the topical-systemic-targeted (TST) protocol for the management of fungal keratitis.

formulations and is USFDA approved for the treatment of invasive aspergillosis and refractory infections with *Fusarium* species and *Scedosporium apiospermum*. Ophthalmic use in topical formulation is off-label and requires reconstitution of the available parenteral formulation to a solution form at a useable concentration of 1% (10 mg/ml) [28,29]. (Table 6) Similar to NTM, VCZ displays a broad spectrum of activity against various species of *Aspergillus, Candida*, *Cryptococcus, Fusarium*, and *Scedosporium.* However, activity against Mucorales is minimal [30, 31]. The dosing schedule of topical VCZ is similar to NTM. VCZ can be administered through multiple routes such as in the form of oral capsules, as intracameral and intrastromal injection and via the intravitreal route. Oral formulation is available in the form of capsules that are rapidly absorbed with a mean time to peak plasma concentration (Tmax) varying between 1.43 and 1.81 h (for 200 mg and 400 mg oral dose respectively) [32,33]. It is administered either 1 h before or 2 h after a meal to avoid poor absorption in acidic medium. Since it is metabolized in the liver, and therefore has a potential to cause hepatotoxicity, following long-term use. A 3 monthly evaluation of liver function tests is therefore routinely advised for patients on long-term VCZ therapy. The efficacy of VCZ as the first-line drug in fungal keratitis is controversial.

Voriconazole is usually the drug of choice in cases of fungal keratitis caused by rare species [34]. Prajna et al. in MUTT 1 trial, demonstrated no advantage of topical VCZ administration over topical NTM [27]. Sharma et al. in a randomized trial, evaluating the role of topical or intrastromal VCZ as an adjunct to topical NTM, found that administration of topical VCZ led to better visual outcomes, with fewer complications. The study included 40 patients with recalcitrant fungal keratitis. Healing rate was found to be 95% in the topical VCZ group compared to 80% in the group that received intrastromal VCZ [35]. Wang et al. evaluated the role of topical VCZ in 84 cases of fungal keratitis in a retrospective, interventional case series. The overall failure rate was 16.67%. Success rate was highest in cases with infections with *Alternaria* species followed by *Aspergillus* species and least for *Fusarium* species cases [36]. The findings were similar to those in MUTT 1, where VCZ results were sub-optimal, especially for cases with the *Fusarium* keratitis.. [27,36]. The role of oral VCZ in fungal keratitis is controversial. Several case reports suggest its usefulness as an adjuvant to topical treatment [37,38]. The pharmacokinetics principle of drug metabolism also supports its role. The use of topical medications alone often leads to periods of sub-therapeutic drug levels, which can be avoided by including oral VCZ in the treatment regimen [39].

Most of the evidence against the use of oral VCZ has come from the MUTT 2 trial. [MUTT2] [22]. The trial compared oral VCZ with placebo as an adjuvant to topical NTM and VCZ therapy, in 240 cases with filamentous fungal keratitis. The rates of corneal perforation, need for penetrating keratoplasty and 3 month BCVA was comparable among the two groups [22]. The major study that suggests the usefulness of oral VCZ is the TST (Topical, Systemic, and Targeted Therapy) protocol by Sharma et al. [40] The study protocol included initial treatment with topical natamycin 5% with oral ketoconazole or voriconazole in ulcers more than 5 mm in size, involving more than 50% of stromal thickness or with an impending perforation. The study included 223 cases of fungal keratitis, which were treated for five years and reported an overall success rate of 79.8%, comparable with other published reports [40]. It is important to note that a subgroup analysis in the MUTT-2 trial did reveal a lower rate of perforations when oral VCZ was used as an adjuvant in *Fusarium* ulcers, although this was not statistically significant [22].

Topical VCZ has minimal side effects in the form of ocular irritation, transient redness and periocular dermatitis [41]. Oral VCZ can cause visual disturbances such as transient visual disturbances, changes in colour vision, and photophobia. Approximately one-third of patients, complain of transient visual changes beginning about 30 min after administration of the drug, subsiding in next 30 min. Rare complications include transient visual hallucinations and confusion [42].

8. Targeted drug delivery

The concept of targeted drug delivery ensures adequate drug delivery to the site of active infection. It is an alternative treatment option in cases of deep fungal keratitis when the response to medical therapy is sub-optimal [21,40,42]. Various methods of targeted drug delivery include intracameral AMB (5–10 mcg/0.1 ml), intracameral voriconazole (50 mcg/0.1 ml), intrastromal Voriconazole; (50-μg/0.1 ml) and intrastromal AMB (0.02 mg/mL). Recently, a solution formulation of NTM known as “Natasol” has been tried in experimental as well as clinical studies [43].

The surgical technique of intrastromal injection, described by

Prakash et al. consists of injecting 50 μg/0.1 ml of reconstituted VCZ solution loaded, in a 1-ml tuberculin syringe with a 30-gauge needle [44]. The needle is inserted obliquely into the cornea from the uninvolved clear area to reach just flush to the ulcer at the mid-stromal level. Five divided doses are given around the ulcer to form a deposit of the drug around the entire circumference of the lesion. This is done in such a manner that the injected drug appears to surround the ulcer along each meridian. In cases of sub-optimal response, three such injections can be given 72 h apart. The exact role and efficacy of targeted drug delivery in fungal keratitis is controversial. We believe targeted therapy, especially intrastromal VCZ is an effective approach for recalcitrant cases of fungal keratitis, not responding to other forms of therapy. The therapy however has some limitations in the form of breaching the natural barriers of infection, risk of deeper spread of infection, iatrogenic spread of fungus at the sites injection, intraocular inflammation, lenticular damage, glaucoma, hyphema, and potential endothelial damage. Similarly, intrastromal injections could lead to the occurrence of new foci of infection, inadvertent anterior chamber entry, and damage to the intraocular structures.

9. Treatment guidelines

It is difficult to formulate a standard guideline for the management of fungal keratitis, that is universally applicable. The authors have recently published "TST protocol" that provides a comprehensive approach for the management of fungal keratitis (Fig. 4). As per the protocol, Natamycin is the first-line therapy in cases of fungal which is started every hourly for the first 48 h, followed by every 2 hourly during the waking hours until complete epithelization is observed. The dose is then reduced to every 4 h period, administered for a period of another 3 weeks. Cycloplegics and analgesics are added to provide symptomatic relief. In cases with inadequate response to NTM at 7-10th day of follow-up, topical VCZ is added, starting every one hourly for the first 48 h and then every two hourly during the waking hours until complete epithelial healing is observed. If the response is still poor after 7–10 days of starting VCZ, intrastromal/intracameral/combined injection of antifungal agents can be given. The authors prefer to use intrastromal VCZ. Intrastromal or intracameral injections can be repeated until a maximum of 4 injections, at an interval of 72 h. Systemic antifungals (oral KTZ; administered 200 mg administered twice daily with meals or oral VCZ; 200 mg twice daily 2 h after a meal) can be included in the treatment regimen if the ulcer size is more than 5 mm or if it involves beyond 50% of corneal stromal depth. Oral therapy can be continued till complete healing of corneal infiltrates is observed. Therapeutic keratoplasty is performed for cases not responding to targeted drug therapy, corneal ulcers associated with thinning wherein intrastromal therapy carries a high risk of corneal perforation, and cases that develop corneal perforation while being on medical treatment [40].

During the 4-year study period of TST, 223 cases were managed using this protocol. *Fusarium* species were the commonest isolated organisms, accounting for 42.2% of all keratitis cases. Other species included *Aspergillus.* (32.8%), *Alternaria.* (6%), *Cladosporium* (3.3%), *Acremonium* (3.3%), *Curvularia* (3.3%), *Candida* (1.3%), *Penicillium* (1.3%) and others (6.1%). The overall treatment success rate with TST protocol was 72.6%. In the intrastromal group (82/223) the success rate was 89% and in the medical management (141/223) group, it was 63.12%. Corneal perforation developed in 15 cases (6.7%) and therapeutic penetrating keratoplasty had to be performed in 36 cases (16.1%) due to treatment failure (perforation/non-healing corneal ulcer).

The overall mean healing time was 41.5 ± 22.2 days, while with intrastromal VCZ injections, it was 36.2 ± 10.7 days. The cases that were treated with only topical and systemic antifungals had a mean healing time of 45.8 ± 27.6 days [40]. Thus, excellent results could be obtained with the TST protocol. However, it is important to remember that use of adjuvant oral antifungals and targeted therapy has yielded variable results in different studies. Besides, the results of MUTT don't favor the use of oral antifungal therapy. Thus, we believe TST protocol is just a guideline, and the treating physician must take a call after considering the local microbiology profile, geographic influences on the occurrence of disease, sensitivity pattern of the organism and most importantly their personal experiences while dealing with cases of fungal keratitis in the past.

10. Rare fungal species: characteristics and preferred drug choices

Apart from the usual fungi implicated in the causation of keratitis, there are some less commonly reported pathogens causing ocular infections. These are usually phytopathogens and are widely distributed in soil, and aquatic systems. Besides causing keratitis, some of these have also been implicated in causing systemic infections such as superficial and deep cutaneous infections, infections of the respiratory system, brain abscess in drug addicts, and contamination of peritoneal dialysis fluids [45,46]. The ttreatment is primarily due to a delayed diagnosis and lack of evidence on susceptibility to routinely used antifungals agents. In general, VCZ is the preferred drug in most such cases of fungal keratitis, and oral antifungals are often helpful. Most of these species have pleomorphic growth patterns on culture with infrequent sporulation. Molecular methods such as, sequencing of Internal Transcribed Spacer (ITS) regions of ribosomal DNA allow for appropriate identification of these rare species.

Lasiodiplodia theobromae, a member of the Botriosphaeriacea family is known to causes keratitis in humans. The first case of keratitis by phytopathogenic L. pseudotheobromae in India was reported by Vanam et al. in a farmer working in mango fields, following penetrating trauma [47]. The identity of fungal pathogen was confirmed by DNA sequencing. Natamycin was found to be ineffective in controlling the progression of disease. In vitro antifungal susceptibility testing revealed lowest MIC levels for Amphotericin B and Voriconazole which correlated with clinical cure.

Didymella gardeniae (earlier known as *Phoma gardenia*) is another uncommon phytopathogen which causes keratitis in humans either following trauma or in association with contact lens use. These infections have been reported in patients on long term topical or systemic immunosuppressant drugs [48,49]. Most studies report cases with *Didymella* species keratitis to require therapeutic keratoplasty [48,50,51]. Miyakubo T et al. reported successful resolution of a case of *Didymella* secies keratitis in a patient on long term steroid therapy, using a combination therapy with topical voriconazole and miconazole [52].

Colletotrichum species including *Colletotrichum coccodes,* Colletotrichum dematium and *Colletotrichum* gloeosporioides [53].*Colletotrichum coccodes* has been implicated to cause both cutaneous phaeohyphomycosis and keratitis, especially following trauma and in immunocompromised patients. Kotwal A et al. reported *Colletotrichum coccodes* keratitis in an immunocompetent patient without any prior history of trauma or co-morbidity [54]. The isolates were found to be sensitive to Amphotericin B and Voriconazole correlating with clinical cure.

Metarrhizium anisopliae is another rare fungus which is commonly used as an agricultural pesticide in many countries around the world [55]. It was earlier believed that the species does not cause infections in humans because of its inability to grow at body temperature. Recent publications however report these fungii to be pathogenic in humans also [56]. Among the cases reported in the literature, variable response to therapy has been documented, some cases completely responding to medical therapy and others progressing to involve sclera, eventually requiring therapeutic keratoplasty.[57].

Pseudallescheria boydii keratitis is another rare yet important fungal pathogen implicated in causing a wide range of ocular as well as extra ocular infections in both immunocompromised and immune-competent patients [58–60]. Prognosis is usually poor in these cases due to inherent resistance of this organism to the existing antifungal agents [61].

Table-7
Outcomes of various forms of antifungal therapy as reported in various studies.

Author	Type of Study	N	Follow-up (months)	Intervention	Indication	Results	Observation
Prajna et al. [27]	RCT	368	3	Topical VCZ (1%) vs. topical NTM (5%)	Filament ous fungi	NTM group had better BCVA, less perforation rate and need for TPK	Predominant inclusion of Fusarium cases (40%) against which VCZ has poor efficacy that could have led to better outcome in NTM group
Arora et al. [45]	Prospe ctive, Rando mized Pilot Study	30	2.5	Group A- 5% NTM (n = 15), Group B 1% VCZ (n = 15)	Fungal keratitis [Aspergil lus (40%), Curvular ia (30.0%)]	Time of resoluti on and improv ement in visual acuity was similar	VCZ has similar efficacy to NTM in Non-Fusarium species
Prajna et al. [26]	Therap eutic Explora tory Clinical Trial	120	3	Topical VCZ (1%) vs. NTM (5%)	Filamentous Fungal keratitis	Visual acuity, scar size, and perforation rate were similar	A trend towards poor visual acuity and scar was seen with VCZ
Wang et al. [46]	Case Control Study	84		NTM 5% vs. FCZ 1%	Fungal keratitis	NTM had higher cure rates than FCZ	
Sharma et al. [47]	RCT	40	3	Topical 1% VCZ Vs. ISVCZ 50 μg/0.1 ml as adjuvant to topical NTM 5%	Ulcer size >2 mm, depth >2/3rd stroma and no response to NTM for 2 weeks	BCVA was better in topical VCZ group	ISVCZ can be tried in recalcitrant cases
Nada et al. [48] 2017	Retrospective	68		Combination therapy of single IS injection of AMB and topical FCZ vs. topical AMB in resistant fungal keratitis	Fungal keratitis	Better recovery and rapid healing with combination therapy	ISAMB is an option in resistant cases
Kalavathy et al. [49]	Prospective Interventional Study	100	NA	Topicalitraconazole 1% vs. topical NTM 5%	Filamentous fungal keratitis	Better Healing rate in NTM Group (72% vs. 60%) in *Fusarium* spp. only. No difference in Aspergillus or Curvularia spp.	NTM is better than Itraconazole in Fusarium cases
Shao et al. [50]	Prospe ctive Controll-ed Clinical Trial	60	NA	ICAMB vs. topical AMB	Fungal keratitis	ICAMB leads to faster healing	ICAMB can be an option for refractory keratomycosis
Sharma et al. [51]	RCT	45	NA	Group I (topical antifungal treatment + or al antifungal); Group II (topical Antifungal treatment + ICAMB + oral antifungal); and Group III (topical antifungal treatment + dr ainage of hypopyon + ICAMB + oral antifungal)	Fungal keratitis	Success rates, healing time and final BCVA was similar between the groups	Increased incidence of cataract in ICAMB group
Rajaram-an et al. [52]	RCT	115	1	Oral KCZ (200 mg BD) + Topical NTM (5%) vs. topical NTM (5%)	2–60 mm^2 ulcer area with depth >50%	Final healing and VA was similar	Healing rate Was better With oral KCZ + topical NTM group
Agrawal et al. [53]	RCT	54	6	Topical ICZ (1%) vs topical and oral ICZ (100 mg BD)	Fungal keratitis	Complete resolution in 77% cases	Response to treatment was poor in the Fusarium spp. group
Parch and et al. [29]	RCT	45	3	Oral and topical VCZ (group 1), oral VCZ and topical NTM (group 2) and oral ICZ and topical NTM (group 3)	Epithelia l defect >5 mm, depth >2/3rd	Healing rate, duration of healing and VA was similar	Systemic VCZ is safe and effective
Prajna et al. [22]	RCT	240	3	Oral VCZ vs. oral placebo in addition to topical antifungal (NTM 5% and VCZ 1%)	Filamentous fungal keratitis with VA <20/400	No benefit of adding oral VCZ	48.7% cases had adverse effects. Elevated LFT and visual disturbances were the most common adverse effects seen.
Nada et al. [48]	Retrospective case series	68		ISAMB + topical FCZ (group A) vs topical AMB (group B)	Group A included resistant cases of fungal keratitis	Resolution rate and healing time was better in ISAMB group ion rate & healing was better in ISAMB Group	ISAMB can be an option in resistant mycotic keratitis in Candida species but a high failure rate was observed in *Fusarium*cases
Shar ma et al. [23]	RCT	50	3	Oral VCZ vs. Oral KCZ	Severe fungal keratitis	BCVA, final mean scar size & healing rate was better with VCZ. Better bioavail ability of VCZ.	Ratio of tear film to serum concent ration of oral VCZ was better than oral KCZ at day 14 and 21 suggest ing better bioavail ability of VCZ

Footnotes.
n- Number of cases; FU- Follow up; RCT- Randomized controlled trial: VCZ- Voriconazole; NTM- Natamycin; BCVA-best corrected visual acuity; logMAR- Logarithm of minimum angle of resolution; TPK- Therapeutic penetrating keratoplasty; IS- Intrastromal; AMB- Amphotericin B; FCZ- Fluconazole; NA- Not available; ICAMB- Intracameral; VA-visual acuity; HPLC- high performance liquid chromatography; LFT- Liver function test; KCZ-ketoconazole; PRK- Photorefractive keratectomy; IS – Intrastromal; IC- Intracameral.

Other less commonly reported, pathogenic fungal species include *Malassezia restricta, Bipolaris species and Coprinellus Radians* [62–64].

10.1. Rose bengal photodynamic therapy (RB-PDAT)

The increasing prevalence of antimicrobial resistance, progression of lesions despite appropriate medical therapy and sub-optimal outcome of grafts performed in eyes with active infection and inflammation, prompted the search for adjunctive treatment options which can either postpone or obviate the need for either an emergency keratoplasty. The use of photodynamic therapy is one such modality, which is currently being evaluated in eyes with progressive forms of keratitis. The technique uses Rose Bengal dye as a photosensitizer, which upon activation reacts with ambient oxygen to produce singlet oxygen and reactive oxygen species causing cellular death [65].

In an experimental study by Arboleda A et al. the vitro effects of rose bengal and riboflavin were compared for photodynamic therapy performed on fungal isolates including *Fusarium solani, Aspergillus fumigatus, Candida albicans* species [66]. Rose Bengal mediated PDT was found to successfully inhibit the growth of all 3 isolates. This was in contrast to the culture plates receiving riboflavin PDT, where unrestricted growth was noted. In a retrospective pilot study by Naranjo A et al., the utility of RB-PDAT was evaluated as an adjunctive treatment for the management of cases with severe infective keratitis [67]. Of the 18 patients enrolled, 5 had fungal etiology including Fusarium species and Curvularia species. Resolution of infection was achieved in 100% eyes, within 38 days of first RB-PDAT treatment. Avoidance of therapeutic penetrating keratoplasty was achieved in 72% patients treated with RB-PDAT. In another study by the same authors, it was found that patients with resistant and severe forms of keratitis, that required therapeutic keratoplasty and had undergone RB-PDAT treatment demonstrated successful therapeutic graft adherence with grafts remaining clear for a comparatively longer duration of time [68]. Another important beneficial effect of RB-PDAT reported is its regressive effect on blood and lymphatics vessels, which is achieved by induction of apoptosis in the vascular endothelial cells [69]. This further ensures improved rates of graft survival after a therapeutic keratoplasty.

As of the now the treatment modality is not being commonly employed by the corneal surgeons. But it has a potential to take an interim position since it helps to avoid the imminent need for a therapeutic graft in an actively inflamed eye, wherein penetrating keratoplasty performed carries an almost 50% risk of failure, in the first 5 years [70].

11. Outcomes

The causative agent plays an important role in determining the outcomes of fungal keratitis. Topical natamycin has been found to yield better results compared to topical Voriconzole especially in *Fusarium* keratitis patients [27], however in non-*Fusarium* cases species the efficacy of topical voriconazole and natamycin is similar [71,72]. Natamycin has also been found to yield better results compared to itraconazole in *Fusarium* cases [75]. Targeted drug delivery in the form of intrastromal injections has been tried in patients with recalcitrant forms of keratitis [73,74,76]. Outcomes of various studies involving various antifungal drugs and their modes of delivery have been summarized in Table 7 [22,23,26,27,29,71,73–75,77–79].

12. Conclusions

The management of Fungal keratitis offers challenges at every step, right from the diagnosis to choosing the type and route of the anti-fungal medication. Natamycin is the usual first drug of choice for filamentous fungal keratitis. Voriconazole holds promise especially in non-*Fusarium* cases and in cases with keratitis attributed to rare pathogens. Role of systemic antifungals is not consistently proven. Alternative therapies in the form of intrastromal injections, have yielded variable results in different groups of patients reported from different parts of the world. Although many randomized trials and protocols have been proposed, it is not possible to recommend a universal protocol for the management of fungal keratitis. The management must be individualized, considering the geographical location, local microbiological profile, the availability of drugs and the treating surgeon's experience. Emerging treatment options such as "photodynamic therapy" and newer methods for the delivery of existing drugs such as contact lens and nano-particle assisted drug delivery hold promising options in the current future, for better management of recalcitrant and progressive cases.

13. Method of literature search

A literature search was performed using PubMed Medline, the Cochrane Library Database, EMBASE and Scopus (from 1960 onwards), using the following terms: Mycotic Keratitis, Anti fungals, Fungal Keratitis, Fungal Corneal Ulcer, Topical Antifungals, Oral antifungals, systemic antifungals, intrastromal antifungals, intracameral antifungals, nanoparticles in ophthalmology, nanoparticles, Natamycin, Voriconazole, Amphotericin B, Itraconazole, Miconazole, Fluconazole, Flucytosine, Caspofungin, Micafungin and contact lenses in keratitis. All relevant articles were included in this review. Priority was given to prospective studies and randomized clinical trials. However, retrospective studies and case reports were included if important. Reference lists from the selected articles were further checked to obtain further relevant articles not included in the electronic database.

References

[1] Srinivasan M. Fungal keratitis. Curr Opin Ophthalmol 2004;15:321–7.
[2] Sahay P, Singhal D, Nagpal R, Maharana PK, Farid M, Gelman R, et al. Pharmacologic therapy of mycotic keratitis. Surv Ophthalmol 2019;64:380–400.
[3] Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a global perspective. Bull World Health Organ 2001;79:214–21.
[4] Gonzales CA, Srinivasan M, Whitcher JP, Smolin G. Incidence of corneal ulceration in Madurai district, South India. Ophthalmic Epidemiol 1996;3:159–66.
[5] Erie JC, Nevitt MP, Hodge DO, Ballard DJ. Incidence of ulcerative keratitis in a defined population from 1950 through 1988. Arch Ophthalmol Chic Ill 1960;111:1665–71. 1993.
[6] Maharana PK, Sharma N, Nagpal R, Jhanji V, Das S, Vajpayee RB. Recent advances in diagnosis and management of Mycotic Keratitis. Indian J Ophthalmol 2016;64:346–57.
[7] Prajna VN, Prajna L, Muthiah S. Fungal keratitis: the Aravind experience. Indian J Ophthalmol 2017;65:912–9.
[8] Lalitha P, Prajna NV, Kabra A, Mahadevan K, Srinivasan M. Risk factors for treatment outcome in fungal keratitis. Ophthalmology 2006;113:526–30.
[9] Mahmoudi S, Masoomi A, Ahmadikia K, Tabatabaei SA, Soleimani M, Rezaie S, et al. Fungal keratitis: an overview of clinical and laboratory aspects. Mycoses 2018;61:916–30.
[10] Niu L, Liu X, Ma Z, Yin Y, Sun L, Yang L, et al. Fungal keratitis: pathogenesis, diagnosis and prevention. Microb Pathog 2020;138:103802.
[11] Bharathi MJ, Ramakrishnan R, Vasu S, Meenakshi R, Palaniappan R. Epidemiological characteristics and laboratory diagnosis of fungal keratitis. A three-year study. Indian J Ophthalmol 2003;51:315–21.
[12] Hagan M, Wright E, Newman M, Dolin P, Johnson G. Causes of suppurative keratitis in Ghana. Br J Ophthalmol 1995;79:1024–8.
[13] Finkelstein A, Holz R. Aqueous pores created in thin lipid membranes by the polyene antibiotics nystatin and amphotericin B. Membranes 1973;2:377–408.
[14] Thomas PA, Kaliamurthy J. Mycotic keratitis: epidemiology, diagnosis and management. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2013;19:210–20.
[15] Podust LM, Poulos TL, Waterman MR. Crystal structure of cytochrome P450 14alpha -sterol demethylase (CYP51) from Mycobacterium tuberculosis in complex with azole inhibitors. Proc Natl Acad Sci U S A 2001;98:3068–73.
[16] Ghannoum MA, Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. Clin Microbiol Rev 1999;12:501–17.
[17] Ryder N s. Terbinafine: mode of action and properties of the squalene epoxidase inhibition. Br J Dermatol 1992;126:2–7.
[18] Ryder NS, Wagner S, Leitner I. In vitro activities of terbinafine against cutaneous isolates of Candida albicans and other pathogenic yeasts. Antimicrob Agents Chemother 1998;42:1057–61.
[19] Patil A, Majumdar S. Echinocandins in ocular therapeutics. J Ocul Pharmacol Ther Off J Assoc Ocul Pharmacol Ther 2017;33:340–52.
[20] Sucher AJ, Chahine EB, Balcer HE. Echinocandins: the newest class of antifungals. Ann Pharmacother 2009;43:1647–57.

[21] Maharana PK, Sharma N, Nagpal R, Jhanji V, Das S, Vajpayee RB. Recent advances in diagnosis and management of Mycotic Keratitis. Indian J Ophthalmol 2016;64:346–57.

[22] Prajna NV, Krishnan T, Rajaraman R, Patel S, Srinivasan M, Das M, et al. Effect of oral voriconazole on fungal keratitis in the mycotic ulcer treatment trial II (MUTT II): a randomized clinical trial. JAMA Ophthalmol 2016;134:1365–72.

[23] Sharma N, Singhal D, Maharana PK, Sinha R, Agarwal T, Upadhyay AD, et al. Comparison of oral voriconazole versus oral ketoconazole as an adjunct to topical natamycin in severe fungal keratitis: a randomized controlled trial. Cornea 2017;36:1521–7.

[24] Qiu S, Zhao G-Q, Lin J, Wang X, Hu L-T, Du Z-D, et al. Natamycin in the treatment of fungal keratitis: a systematic review and Meta-analysis. Int J Ophthalmol 2015;8:597–602.

[25] Lalitha P, Vijaykumar R, Prajna NV, Fothergill AW. In vitro natamycin susceptibility of ocular isolates of Fusarium and Aspergillus species: comparison of commercially formulated natamycin eye drops to pharmaceutical-grade powder. J Clin Microbiol 2008;46:3477–8.

[26] Prajna NV, Mascarenhas J, Krishnan T, Reddy PR, Prajna L, Srinivasan M, et al. Comparison of natamycin and voriconazole for the treatment of fungal keratitis. Arch Ophthalmol Chic Ill 1960 2010;128:672–8.

[27] Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Prajna L, Srinivasan M, et al. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. JAMA Ophthalmol 2013;131:422–9.

[28] Bunya VY, Hammersmith KM, Rapuano CJ, Ayres BD, Cohen EJ. Topical and oral voriconazole in the treatment of fungal keratitis. Am J Ophthalmol 2007;143:151–3.

[29] Parchand S, Gupta A, Ram J, Gupta N, Chakrabarty A. Voriconazole for fungal corneal ulcers. Ophthalmology 2012;119:1083.

[30] Diekema DJ, Messer SA, Hollis RJ, Jones RN, Pfaller MA. Activities of Caspofungin, itraconazole, posaconazole, ravuconazole, voriconazole, and amphotericin B against 448 recent clinical isolates of filamentous fungi. J Clin Microbiol 2003;41:3623–6.

[31] Pfaller MA, Messer SA, Boyken L, Rice C, Tendolkar S, Hollis RJ, et al. Global trends in the antifungal susceptibility of Cryptococcus neoformans (1990 to 2004). J Clin Microbiol 2005;43:2163–7.

[32] Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob Agents Chemother 2002;46:2546–53.

[33] Purkins L, Wood N, Greenhalgh K, Allen MJ, Oliver SD. Voriconazole, a novel wide-spectrum triazole: oral pharmacokinetics and safety. Br J Clin Pharmacol 2003;56:10–6.

[34] Sahay P, Goel S, Nagpal R, Maharana PK, Sinha R, Agarwal T, et al. Infectious keratitis caused by rare and emerging micro-organisms. Curr Eye Res 2020:1–13.

[35] Sharma N, Agarwal P, Sinha R, Titiyal JS, Velpandian T, Vajpayee RB. Evaluation of intrastromal voriconazole injection in recalcitrant deep fungal keratitis: case series. Br J Ophthalmol 2011;95:1735–7.

[36] Wang LY, Xu ZZ, Zhang JJ, Sun ST, Li J, Yu XF, et al. [Topical voriconazole as an effective treatment for fungal keratitis]. Zhonghua Yan Ke Za Zhi Chin J Ophthalmol 2016;52:657–62.

[37] Freda R. Use of oral voriconazole as adjunctive treatment of severe cornea fungal infection: case report. Arq Bras Oftalmol 2006;69:431–4.

[38] Jones A, Muhtaseb M. Use of voriconazole in fungal keratitis. J Cataract Refract Surg 2008;34:183–4.

[39] Thiel MA, Zinkernagel AS, Burhenne J, Kaufmann C, Haefeli WE. Voriconazole concentration in human aqueous humor and plasma during topical or combined topical and systemic administration for fungal keratitis. Antimicrob Agents Chemother 2007;51:239–44.

[40] Sharma N, Sahay P, Maharana PK, Singhal D, Saluja G, Bandivadekar P, et al. Management algorithm for fungal keratitis: the TST (topical, systemic, and targeted therapy) protocol. Cornea 2019;38:141–5.

[41] Sahay P, Asif MI, Maharana PK, Titiyal JS. Periocular contact dermatitis with use of topical voriconazole 1% in mycotic keratitis. BMJ Case Rep 2018;2018.

[42] Sahay P, Singhal D, Nagpal R, Maharana PK, Farid M, Gelman R, et al. Pharmacologic therapy of mycotic keratitis. Surv Ophthalmol 2019;64:380–400.

[43] Mimouni M, Tam G, Paitan Y, Kidron D, Segev F. Safety and efficacy of intrastromal injection of 5% natamycin in experimental fusarium keratitis. J Ocul Pharmacol Ther Off J Assoc Ocul Pharmacol Ther 2014;30:543–7.

[44] Prakash G, Sharma N, Goel M, Titiyal JS, Vajpayee RB. Evaluation of intrastromal injection of voriconazole as a therapeutic adjunctive for the management of deep recalcitrant fungal keratitis. Am J Ophthalmol 2008;146:56–9.

[45] Bennet Ashely, Ponder Michelle M, Garcia-Diaz Julia. Phoma infections: classification, potential food sources, and their clinical impact. Microorganisms 2018;6(3):58.

[46] Reddy M, Venugopal R, Prakash PY, Kamath YS. Corneal ulcer due to a rare coelomycete fungus *Chaetomium strumarium*: case report and global review of *Chaetomium* keratomycosis. Indian J Ophthalmol 2017 Sep;65(9):871–4.

[47] Vanam HP, Ather M, Madhura KS, Rudramurthy SM. First report of *Lasiodiplodia pseudotheobromae* keratitis susceptible to voriconazole in an Indian mango grower. Access Microbiol 2019 Aug 16;1(6):e000055.

[48] McElnea E, Farrell S, Lynch B, Bishop K, Mullen D, Borman A, et al. A rare case of fungal keratitis: diagnosis and management. JMM Case Rep 2015;2:e000091.

[49] Errera MH, Barale PO, Nourry H, Zamfir O, Guez A, Warnet JM, et al. Usefulness of voriconazole in treatment of Phoma glomerate after penetrating injury. J. Fr. Ophthalmol. 2008;31:62–6.

[50] Rishi K, Font RL. Keratitis caused by an unusual fungus, Phoma species. Cornea 2003;22(2):166–8.

[51] Kumar P, Thomas S, Papagiannuli E, Hardman S, Jenkins D, Prydal J. A case of Phoma fungal keratitis in a contact lens user. JRSM Open 2015;6(3):1–2.

[52] Miyakubo T, Todokoro D, Makimura K, Akiyama H. Fungal keratitis caused by *Didymella gardeniae* (formerly *Phoma gardeniae*) successfully treated with topical voriconazole and miconazole. Med Mycol Case Rep 2019 Apr 27;24:90–2.

[53] Buchta V, Nekolová J, Jirásková N, Bolehovská R, Wipler J, Hubka V. Fungal keratitis caused by colletotrichum dematium: case study and review. Mycopathologia 2019 Jun;184(3):441–53.

[54] Kotwal A, Biswas D, Kakati B, Bahadur H, Gupta N. Non traumatic keratitis due to colletotrichum coccodes: a case report. J Clin Diagn Res 2015 Feb;9(2):DD01–2.

[55] Motley WW, Melson AT, Mortensen JE. Pediatric Metarrhizium anisopliae keratitis. J. AAPOS 2011;15(1):101–3.

[56] Amiel H, Chohan AB, Snibson GR, Vajpayee R. Atypical fungal sclerokeratitis. Cornea 2008;27(3):382–3.

[57] Showail MJ, Kus JV, Tsui GK, Chew HF. Fungal keratitis caused by *Metarhizium anisopliae complex*. Med Mycol Case Rep 2017 Jun 23;17:28–30.

[58] Izadi A, Soleimani M, Dos Santos CO, Tehupeiory-Kooreman MC, Daie Ghazvini R, Hashemi SJ, Gramishoar M, Aminizadeh M, Abedinifar Z, Verweij PE, Khodavaisy S. Fungal keratitis caused by Pseudallescheria boydii: clinical and mycological characteristics. J Ophthalmic Inflamm Infect 2021 Sep 24;11(1):30.

[59] Sicilia ML, Lacomba MS, Cuesta FS, Pedraza RS, Gomez TN, Roman MC. Scedosporium apiospermum keratitis. Rev Iberoam De Micol 2003;20:68–70.

[60] Rathi HS, Venugopal A, Rengappa R, Ravindran M. Scedosporium keratitis: an experience from a tertiary eye hospital in South India. Cornea 2016;35(12):1575–7.

[61] Tabatabaei SA, Tabatabaei M, Soleimani M, Tafti ZF. Fungal keratitis caused by rare organisms. J Curr Ophthalmol 2018;30(1):91–6.

[62] Suzuki T, Hori N, Miyake T, Hori Y, Mochizuki K. Keratitis caused by a rare fungus, Malassezia restricta. Jpn J Ophthalmol 2007 Jul-Aug;51(4):292–4.

[63] Pai HV, Jamal E, Yegneswaran PP. Corneal ulcer due to a rare pleosporalean member of the genus Bipolaris following cow tail injury to the eye: a case report and review of literature. Indian J Ophthalmol 2017 May;65(5):403–5.

[64] Lu X, Wang X, Zhang L, Li X, Qi X. Rare fungal keratitis caused by Coprinellus Radians. Mycopathologia 2020 Apr;185(2):389–94.

[65] Dai T, Fuchs BB, Coleman JJ, et al. Concepts and principles of photodynamic therapy as an alternative antifungal discovery platform. Front Microbiol 2012;3:120.

[66] Arboleda A, Miller D, Cabot F, Taneja M, Aguilar MC, Alawa K, Amescua G, Yoo SH, Parel JM. Assessment of rose bengal versus riboflavin photodynamic therapy for inhibition of fungal keratitis isolates. Am J Ophthalmol 2014 Jul;158(1):64–70.e2.

[67] Naranjo A, Arboleda A, Martinez JD, Durkee H, Aguilar MC, Relhan N, et al. Rose bengal photodynamic antimicrobial therapy for patients with progressive infectious keratitis: a pilot clinical study. Am J Ophthalmol 2019;208:387–96.

[68] Martinez JD, Arboleda A, Naranjo A, Aguilar MC, Durkee H, Monsalve P, et al. Long-term outcomes of riboflavin photodynamic antimicrobial therapy as a treatment for infectious keratitis. Am J Ophthalmol Case Rep 2019;15:100481.

[69] Martinez JD, Naranjo A, Amescua G, Dubovy SR, Arboleda A, Durkee H, et al. Human corneal changes after rose bengal photodynamic antimicrobial therapy for treatment of fungal keratitis. Cornea 2018;37(10):e46–8.

[70] Kirkness CM, Ficker LA, SteeleADM, et al. The role of penetrating keratoplasty in the management of microbial keratitis. Eye 1991;5:425–31.

[71] Arora R, Gupta D, Goyal J, Kaur R. Voriconazole versus natamycin as primary treatment in fungal corneal ulcers. Clin Exp Ophthalmol 2011;39:434–40.

[72] Wang D-M, Chen G-S, Huang M-H. Observation of therapeutical effect of natamycin in fungal corneal ulcer. Int J Ophthalmol 2010;10:744–5.

[73] Sharma N, Chacko J, Velpandian T, Titiyal JS, Sinha R, Satpathy G, et al. Comparative evaluation of topical versus intrastromal voriconazole as an adjunct to natamycin in recalcitrant fungal keratitis. Ophthalmology 2013;120:677–81.

[74] Nada WM, Al Aswad MA, El-Haig WM. Combined intrastromal injection of amphotericin B and topical fluconazole in the treatment of resistant cases of keratomycosis: a retrospective study. Clin Ophthalmol Auckl NZ 2017;11:871–4.

[75] Kalavathy CM, Parmar P, Kaliamurthy J, Philip VR, Ramalingam MDK, Jesudasan CAN, et al. Comparison of topical itraconazole 1% with topical natamycin 5% for the treatment of filamentous fungal keratitis. Cornea 2005;24:449–52.

[76] Shao Y, Yu Y, Pei C-G, Tan Y-H, Zhou Q, Yi J-L, et al. Therapeutic efficacy of intracameral amphotericin B injection for 60 patients with keratomycosis. Int J Ophthalmol 2010;3:257–60.

[77] Sharma N, Sankaran P, Agarwal T, Arora T, Chawla B, Titiyal JS, et al. Evaluation of intracameral amphotericin B in the management of fungal keratitis: randomized controlled trial. Ocul Immunol Inflamm 2016;24:493–7.

[78] Rajaraman R, Bhat P, Vaidee V, Maskibail S, Raghavan A, Sivasubramaniam S, et al. Topical 5% natamycin with oral ketoconazole in filamentous fungal keratitis: a randomized controlled trial. Asia-Pac J Ophthalmol Phila Pa 2015;4:146–50.

[79] Agarwal PK, Roy P, Das A, Banerjee A, Maity PK, Banerjee AR. Efficacy of topical and systemic itraconazole as a broad-spectrum antifungal agent in mycotic corneal ulcer. A preliminary study. Indian J Ophthalmol 2001;49:173.